REMARKS/ARGUMENTS

The Pending Claims

Claims 1, 3, 4, 6-17, 32, and 33 are currently pending and are directed to a method of treating a condition treatable by the inhibition of vacuolar-type (H+)-ATPase.

Summary of the Claim Amendments

Claims 2 and 5 have been canceled as unnecessary in view of the amendments to claim 1. Claims 1 and 6 have been amended to recite a method of treating a condition treatable by the inhibition of vacuolar-type (H+)-ATPase, in which the condition is urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease. New claims 32 and 33 have been added. These amendments are supported by the specification at, for example, page 20, lines 17-31. No new matter has been added by way of these amendments.

Summary of the Office Action

Claims 1-7 and 12-17 stand rejected under 35 U.S.C. § 103(a) as obvious over McKee et al. (*J. Org. Chem.*, 63: 7805-7810 (October 2, 1998)) in view of Oku et al. (WO 99/21835) and Simon et al. (U.S. Patent Publication No. 2002/0042079). Claims 8-11 stand rejected under 35 U.S.C. § 103(a) as obvious over McKee et al. in view of Oku et al. and Simon et al. and further in view of Holt et al. (WO 93/18652) and Yamamoto et al. (*Cell Struct. Funct.* 23: 33-42 (1998)). Reconsideration of the pending claims is respectfully requested.

Discussion of the Obviousness Rejections

McKee et al., Oku et al., and Simon et al.

Claims 1-7 and 12-17 are rejected as obvious over McKee et al. in view of Oku et al. and Simon et al. The Office Action contends that McKee et al. discloses lobatamides A-D as having anti-tumor activity, while conceding that McKee et al. does not disclose the administration of apicularen A or B, the claimed amounts, or treatment of intra-organellar acidification of intracellular organelles. The Office Action asserts that it would have been obvious to use the claimed compounds in a method of treating cancer because McKee et al.

describes the cytotoxicity of lobatamides A-D. The Office Action further contends that while other pathways are possible for the treatment of cancers, administration of the compounds disclosed by McKee et al. would "obviously meet the claims" because Oku et al. teaches that it is known in the art to treat cancers by inhibiting vacuolar-type (H+)-ATPase and Simon et al. teaches that it is known in the art to enhance the treatment of cancer by reducing acidification within organelles. The Office Action concludes the pending claims would have been obvious "because a claim for the administration of the same compound to the same population is not rendered patentable by the discovery of a new mechanism by which the treatment works." This rejection is respectfully traversed.

The claims have been amended to recite a method of treating a condition treatable by the inhibition of vacuolar-type (H+)-ATPase, in which the condition is urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease. McKee et al. discloses the structures and cytotoxicity data for certain lobatamides (i.e., compounds **1-6**). As McKee et al. is relied upon for the (direct or indirect) treatment of cancer, this reference does not recite all of the elements of the pending claims.

Moreover, the mere disclosure in McKee et al. of anticancer activity in connection with the recited compounds does not render obvious the therapeutic inhibition of vacuolar-type (H+)-ATPase for the treatment of urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease. As stated in the Office Action, "The examiner fully agrees that 'the mere fact that an agent may be cytotoxic to cancer cells does not necessarily mean that the mechanism by which the compound is cytotoxic is by the inhibition of vacuolar-type (H+)-ATPase, that the compound is able to inhibit vacuolar-type (H+)-ATPase'" (see Office Action, page 5, second full paragraph). McKee et al. does not teach or suggest the inhibition of vacuolar-type (H+)-ATPase or treating urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease. One skilled in the art would not have understood from McKee et al. that the compounds described in the claims would have been useful for treating any of the claimed conditions, nor would one skilled in the art have had any reasonable expectation of success to treat any such claimed condition with the compounds claimed in view of McKee et al.

Oku et al. describes structurally unrelated quinoline derivatives as (H+)-ATPase inhibitors. Oku et al. further discloses that since the compounds inhibit vacuolar-type (H+)-ATPase, they are useful for the prevention and/or treatment of several disorders (page 15, line 30, through page 16, line 21). However, Oku et al. does not disclose a method of treating a condition treatable by the inhibition of vacuolar-type (H+)-ATPase, in which the condition is urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease comprising a compound of formulae (I) and (IF), as recited in the pending claims.

Simon et al. relates to a method for monitoring the likelihood or onset of multidrug resistance in mammals and the identification and monitoring of agents useful for minimizing multidrug resistance, particularly with respect to the treatment of cancer (paragraph [0073]). However, Simon et al. does not disclose a method of treating a condition treatable by the inhibition of vacuolar-type (H+)-ATPase, in which the condition is urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease comprising a compound of formulae (I) and (IF), as recited in the pending claims.

The cited references thus fail to disclose a method for treating urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease using the compounds of formulae (I) and (IF) as claimed. Accordingly, Applicant submits that amended claims 1, 3, 4, 6, 7 and 12-17 (and new claims 32 and 33) would not have been obvious to one of ordinary skill in the art in view of McKee et al. alone or McKee et al. in view of Oku et al. and/or Simon et al. Therefore, the obviousness rejection based on these references should be withdrawn.

McKee et al., Oku et al., Simon et al., Holt et al., and Yamamoto et al.

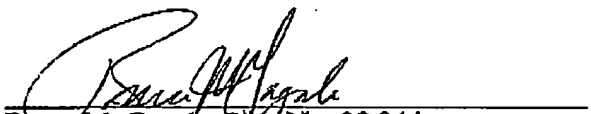
Claims 8-11 are rejected as allegedly obvious over McKee et al. in view of Oku et al. and Simon et al. and further in view of Holt et al. and Yamamoto et al. The disclosures of McKee et al., Oku et al., and Simon et al. have been discussed above. Holt et al. purportedly discloses the administration of bafilomycins, which inhibit (H+)-ATPase, for the treatment of cancer. Yamamoto et al. allegedly discloses the equivalent activities of bafilomycin A_1 and concanamycins regarding vacuolar (H+)-ATPase inhibition.

For the reasons discussed above, the disclosure of McKee et al. alone or in combination with Oku et al. and Simon et al. does not render the invention defined by claims 8-11 obvious. Claims 8-11 ultimately are dependent on claim 1, and must include a compound of formulae (I) or (IF). Holt et al. and Yamamoto et al. disclose at best bafilomycins, bafilomycin A1 and concanamycin, -- compounds that are structurally unrelated to the class of compounds disclosed herein as formulae (I) and (IF). The compounds of Holt et al. and Yamamoto et al. exhibit (H+)-ATPase inhibition for the treatment of cancer. Thus, Holt et al. and Yamamoto et al. do not disclose a method of treating a condition treatable by the inhibition of vacuolar-type (H+)-ATPase, in which the condition is urinary acidification, bone resorption, osteoporosis, fertility, angiogenesis, glaucoma, or Alzheimer's disease comprising a compound of formulae (I) and (IF), as recited in the pending claims, and do not bridge the gap in the differences between McKee et al., Oku et al., and Simon et al. and the claimed method. Accordingly, claims 8-11 would not have been obvious for one skilled in the art in view of these references, and the rejection should be withdrawn.

Conclusion

Applicant respectfully submits that the application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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